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A 37-year-old man referred for assistance with persistent asthma, atopic dermatitis, and chronic conjunctivitis

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At the conclusion of this activity, participants should be able to:

- Discuss the various signs and symptoms of chronic eye allergy
- Summarize available therapeutic options as well as possible ocular complications related to the management of atopic keratoconjunctivitis (AKC)

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Introduction

The allergist or clinical immunologist will successfully review the case of a chronic form of allergic conjunctivitis in a patient with atopy and (1) recognize the common signs and symptoms of chronic eye allergy and (2) appreciate the ocular complications from ongoing treatment for atopic disorders.

Clinical Vignette

A 37-year-old man is referred to the allergy service for assistance with his persistent asthma, eczema, and chronic conjunctivitis.

Since childhood, his asthma and allergic rhinitis has been well controlled with an inhaled corticosteroid, long-acting β-agonist therapy, and intranasal corticosteroids. He has had multiple courses of oral corticosteroids but was never admitted to the hospital. While living in Italy, his eczema and asthma had been controlled, but he had seasonal exacerbations of chronic red eyes, tearing, droopy upper eyelids (at times with a glassy appearance), nasal congestion, and a runny nose that never completely resolved. His symptoms became worse during college. His visual acuity decreased after graduating, and he currently works in an accounting department with more than 8 hours a day of computer work. He uses antihistamines continually to control his sneezing. He has increased ocular discomfort, has started to squint constantly, and has mild blurring of vision and increasing sensitivity to light without pain.

The patient's ophthalmologist noted increased curvature of the left cornea with mild keratitis. The ophthalmologist has been treating him for the past 12 years because he has had increasing involvement of scaling around both eyes that has led to crusting on the eyelids, involving the eyelashes. He recently started using over-the-counter ocular lubricants on a regular basis because his eyes have started to feel gritty. He states that the "itch" is extremely bothersome, and constantly rubs his eyes and frequently has to blink.

The patient also has a stringy mucus discharge treated with multiple courses of topical corticosteroids. Baseline intraocular pressure was 16 mm in the left eye and 22 mm in the right eye with some lens opacification in the posterior pole of the right eye after topical treatment with limited injection. His eczema has required ongoing oral steroid treatment. He has developed a progressive ropey ocular discharge in the morning. The patient has increasing complaints of eczema, and his asthma has started to require increasing doses of inhaled bronchodilators.

Family History

The patient was born in Italy and moved at 8 years of age to the United States. His father has asthma; his brother and sister have atopic dermatitis; his parents and several siblings have allergic rhinoconjunctivitis; and his mother and maternal grandmother have glaucoma. Cataracts had developed in the 2 sets of grandparents.

Physical Examination

There is increased redness and swelling around both eyes and cheeks, with increased creases below his eyes and a peculiar absence of the lateral eyebrows with eyelids that are slightly asymmetrical. There is thickening of both lids with redness, fissuring, and swelling (Fig 1). The conjunctiva has diffuse fine areas of pinhead-shaped and pinhead-sized lesions of the upper and lower tarsal conjunctiva, diffuse multiple blood vessels and increased thickness of the clear portions of the conjunctiva, and a white stringy semisolid thread of white mucus in the inferior fornix. The upper right eyelid touches the iris, with the left upper eyelid touching the pupil.

The ophthalmologist's records note small areas of epithelium loss from the cornea with the application of fluorescein staining. There are white lines running across the inside portions of the lower palpebral portion of the conjunctiva. There is noted thinning of the eyelashes, with some that appear to be turning inward and irritating the ocular surface.

The nasal mucosa is pale and boggy, with a stringy nasal opaque to yellow mucus covering the posterior oropharynx. The ears demonstrate cerumen partly occluding the left tympanic membrane. There are no pretragal or submental nodes. The lung examination is significant for mild bilateral end-expiratory wheezes with a prolonged expiratory phase of respiration; no nasal flaring or accessory muscle use is appreciated. Skin examination is significant for thickened, pigmented skin in the antecubital fossa. The rest of the physical examination is normal.

Testing

The patient's white blood cell count was 7,800 cells/mm^3 with 1,260 eosinophils/mm^3 compared with 10,100 cells/mm^3 with 220 eosinophils/mm^3 6 weeks previously on 40 mg of prednisone. Total serum IgE was 836 IU/mL. Eosinophils and neutrophils in the H&E stained stringy exudate from the eye. Spirometry demonstrated a forced expiratory volume in 1 second of 74% (83% after using the bronchodilator). Delayed skin tests to candida and tuberculin did not show reactivity at 24, 48, and 72 hours. Skin prick testing showed normal, immediate responses to histamine and saline, with minimal reactions to grass and weed pollen and moderate reactions to oak, maple, and birch. There was strong reactivity to dust mite.

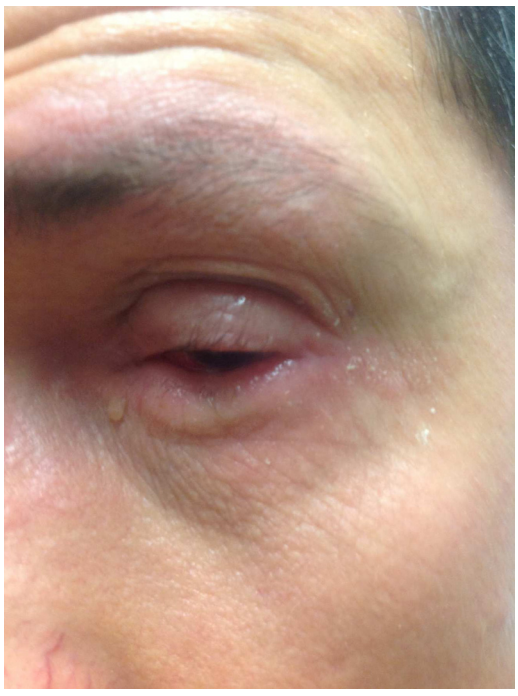

Figure 1. This patient has increased redness and swelling around the eyes and cheek, with increased creases below his eyes and a peculiar absence of the lateral eyebrows (de Hertoghe sign), with eyelids that are slightly asymmetrical. There is a loss of eyelashes and swelling along the rim of the eyelid, indicative of madarosis and blepharitis, respectively. Although not seen in this photograph, many patients with chronic forms of conjunctivitis associated with eosinophilic infiltration can develop Horner-Trantas dots (points) that contain eosinophils and neutrophilic debris along the limbus of the eye.

Table 1
Atopic vs vernal conjunctivitis

	Vernal	Atopic
Age	younger	older
Sex predilection	male	nil
Duration of disease	self-limiting	chronic
Time of year	spring	perennial
Conjunctival involvement	superior tarsus	inferior tarsus
Cicatrization	absent	common
Cornea[a]	shield ulcer	persistent epithelial defect
Corneal scarring	mild	severe
Corneal vascularization	rare	common
Allergen sensitivity	50% positive skin test reaction (most often to house dust)	>90% positive skin test reaction to all seasonal aeroallergens

[a]When chronic conjunctivitis concomitantly involves the cornea, it is termed *keratoconjunctivitis*.

Discussion

The patient clearly has a spectrum of atopic disease affecting the classic target organs of the skin, nose, lungs, and eyes. The most immediate problem involves the ocular surface with a recent acute episode that might involve an acute bacterial infection overlying a form of chronic conjunctivitis called *atopic keratoconjunctivitis* (AKC). AKC is in contrast with vernal keratoconjunctivitis (VKC), which is seen more commonly in children (Table 1).

Chronic conjunctivitis is considered for any conditions lasting longer than 3 weeks, because that is the upper limit for cases of viral infections and most bacterial infections to resolve without treatment. The patient has a form of chronic conjunctivitis with an acute infectious episode.

Atopic keratoconjunctivitis is a debilitating condition owing to its ability to cause visual loss from corneal complications.[1] AKC is at the severe end of a spectrum of allergic conjunctival diseases that includes several subtypes: seasonal (or intermittent, <4 weeks; called *seasonal allergic conjunctivitis*), perennial (or persistent, >4 weeks) allergic conjunctivitis, AKC, VKC, and giant papillary conjunctivitis (GPC). In seasonal or perennial allergic conjunctivitis, proliferative changes seen in the more severe forms of allergic conjunctival disease are absent. AKC is clinically associated with keratoconus, retinal detachment, and the formation of giant papillae. Keratoconus is an excessive curvature to the cornea that interferes with the proper focus of light and thus leads to visual impairment that can require a corneal transplant. VKC is characterized by proliferative changes in the conjunctiva and corneal lesions, such as superficial punctate keratitis, corneal erosions, corneal ulcers, or corneal plaques, occurring primarily in the pediatric population. In GPC, corneal lesions are absent, but proliferative changes are seen in the upper palpebral conjunctiva that are thought to occur by mechanical irritation from the contact of foreign bodies, such as contact lenses, ocular prosthesis, or surgical sutures.[2]

Ocular findings differ in their specificity for AKC. Giant papillae, limbal proliferation, and shield ulcers are highly specific for AKC. Conjunctival edema and follicles, papillary hyperplasia, and corneal epithelial abrasions (corneal erosions and exfoliated superficial punctate keratitis) are intermediately specific for AKC.[2]

Atopic keratoconjunctivitis has been thought to be relatively uncommon but may be more apparent in clinical practice because approximately 5% of patients with eczema have some ocular involvement.[3,4]

Atopic keratoconjunctivitis is a highly symptomatic disorder with severe itching, watering, stickiness, and redness of the eyelids and eye. These symptoms sometimes cause ocular pain. The symptoms of redness and itching that overlap with dry eye disease can be objectively measured with the Ocular Surface Disease Index validated instrument that can be used in an office setting (eSupplement).[5] However, if pain mimicking a corneal abrasion is noted, then an immediate consultation with an ophthalmologist is warranted. There is usually facial eczema involving the eyelids, and the lid margins show blepharitis (a chronic inflammation of the lash follicles and meibomian glands) spilling over and causing additional inflammation of the conjunctival surface (Table 2). The skin of the eyelids may exhibit induration, scaling, and lichenification. The lid margins are thickened and hyperemic, posteriorly rounded, and sometimes keratinized, and the lid anatomy may be distorted with what is seen as a droopy eyelid.

Disease of the ocular surfaces involves changes in the tear biofilm as clearly demonstrated with increases in IgE antibody, histamine, bradykinin, tryptase, interferon-γ, interleukin-6, and interleukin-10 occurring over a 24-hour period with typical early- and late-phase reaction mediator release in conjunctival provocation studies.[6] The combined effects of these mediators yield the various signs and symptoms of allergic conjunctivitis, including redness and itching, and tearing overlaps the early- and late-phase allergic reactions, thus requiring the combination of various chronic ocular allergy treatments to maximize therapeutic effects.[7–9]

Table 2
Characteristics of chronic nonatopic blepharitis[a]

	Sign	Anterior blepharitis		
		Staphylococcal	Seborrheic	Posterior blepharitis
Lashes	deposit	hard	soft	
	loss	++	+	
	distorted or trichiasis	++	+	
Lid margin	ulceration	+		
	notching	+		++
Cyst	acute hordeolum	++		
	meibomian			++
Conjunctiva	phlycten	+		
Tear film	foaming			++
	dry eye	+	+	++
Cornea	punctate erosions	+	+	++
	vascularization	+	+	++
	infiltrates	+	+	++
Associated dermatitis		atopic	seborrheic	acne rosacea

[a]Blepharitis (inflammation of the eyelid) may involve crusting, redness, and swelling of the anterior lid margin. Involvement of the periocular tissue can take up several forms, with significant involvement of the eyelids, as noted in chronic blepharitis, molluscum contagiosum, and atopic keratoconjunctivitis, which also extensively involve the conjunctival surface. Examination of the posterior lid margin shows a squared (normal) or rounded margin (indicating chronic disease) in ocular allergic disorders. In chronic lid margin disorders, the meibomian gland orifices are unevenly dilated, and their secretion is yellow and semisolid (it may even form a solid wax) in contrast to the normal clear fluid that is produced.

Table 3
Considerations for referral to and from an allergist and an ophthalmologist

Referral from an allergist/clinical immunologist to an ophthalmologist is warranted when
Any patient has used ocular steroids for >2 wk
There are any persistent qualities of any ocular complaint
There is consideration of strong topical steroids or systemic steroids
There is ciliary flush, suggesting uveitis
Referral from an ophthalmologist to an allergist/clinical immunologist is warranted when
Systemic evaluation of atopy (eg, eczema, rhinitis, sinusitis, asthma) is required
There is consideration of systemic immunomodulation (immunotherapy)
Systemic assessment of an autoimmune process is necessary
There are persistent moderate to severe clinical allergic ocular complaints
The patient requests it, in accordance with the physician's treatment plan

However, there also appears to be a barrier effect on the ocular surface in a patient with AKC, similar to eczema, because looser tight junctions between epithelial cells have been noted that may facilitate allergen penetration.[10]

When the cornea is involved, blepharospasm from photophobia and blurring of vision cause the patient to require time in the morning to get acclimated. Pain is not a feature of the acute forms of ocular allergy but can be involved in the more chronic forms when they involve the cornea, mimicking a corneal abrasion. This should generate an immediate referral to an ophthalmologist (Table 3). There is no preauricular lymphadenopathy, which is more commonly seen in viral conjunctivitis. The description of a glassy appearance suggests the presence of conjunctival edema with hyperemia because the swelling of the bulbar surface causes it to be more diffusely pink than red.

Alterations in the volume or quality of the tear film can cause severe dry eye. Corneal plaque similar to that of vernal disease is sometimes seen. Associations between AKC and eye rubbing, keratoconus, atopic cataract, and retinal detachment are recognized.

Exudates can take different forms. The most common type of exudate as manifested in this patient's most recent form of conjunctivitis was mucopurulent (or catarrhal), representing a mixture of mucous and pus that clearly suggests a bacterial infection. In some chronic forms of allergic conjunctivitis, such as VKC, a thick, tenacious mucoid exudate that can be peeled off as a string from the conjunctival surface occurs; this commonly has eosinophils when stained with Giemsa.

An important component of the eye examination is the presence of ptosis (a drooping or falling of the upper or lower eyelid), because it notes the position of the eyelid in relation to the pupil. The normal eye has the lid just touching the iris but not the pupil, whereas the exophthalmic eye has the eyelid not touching the iris at all, displaying the white of the sclera between the eyelid and the iris. In ptosis, the eyelid covers most of the upper iris and may cover some of the pupil. This suggests additional pathology to be sought in the eyelid or orbit with the formation of papillae on the upper eyelid, oculomotor nerve palsy, or aging.

The patient's history of severe ocular involvement with a droopy eyelid or ptosis when living in Italy suggests the possibility of VKC or an early form of atopic conjunctivitis (Table 1). The involvement of the cornea in AKC is more commonly reported in older patients. The absence of contact lens use or a foreign body also makes the diagnosis of GPC unlikely. GPC is more commonly associated with a milder form of ocular pruritus than is VKC. In VKC, enlarged papillae up to 7 to 8 mm in diameter may form on the tarsal conjunctivae. These papillae are a classic hallmark of this disease and form a cobblestone appearance.

As with eczema, there is a tendency for increased colonization with cutaneous staphylococcus on the skin and on or around the eyes and eyelids with AKC. The development of staphylococcal blepharitis involves soft scales around lash roots that eventually lead to madarosis and trichiasis. The primary treatment for blepharitis is focused on lid hygiene, such as scrubbing the eyelids with nontearing solutions (eg, a baby shampoo) with a cotton swab or warm disposable towelettes. In more extensive disease, the anterior lid margin may have ulcerations, notching, and microabscesses that eventually evolve to become cystic lesions (eg, hordeolums or styes). Patients often complain of dry eye symptoms because the tear biofilm is altered. The conjunctiva commonly involves papillae and phlyctens (pinkish yellow nodules in the cornea or conjunctiva that usually develop into an ulcer). Fluorescein examination of the corneal surface demonstrates punctate erosions and marginal infiltrates. It is commonly associated with eczema of the eyelids.

Treatment of AKC

The treatment regimen for AKC is multidisciplinary because it also involves treatment of the ocular surface and the concomitant

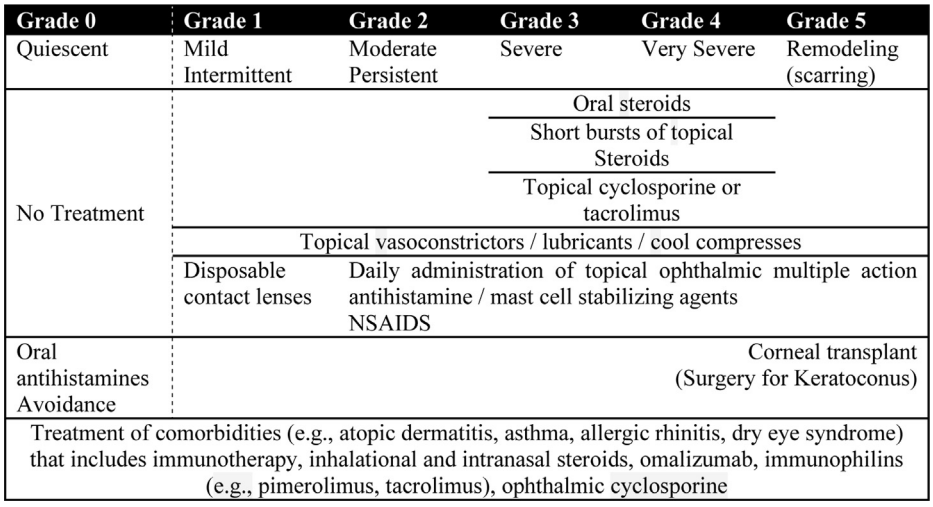

Figure 2. A stepwise approach to the treatment of atopic keratoconjunctivitis until adequate control of the condition is achieved. A stepwise approach reflects the intensity of cellular involvement and the mediators that are in the tear biofilm from the allergic inflammation. Topical therapeutics represents the mainstay of treatment. Consider discontinuation of oral antihistamines because of their potential anticholinergic effect, which will increase drying of the surface. This is important if tear film instability is already present. Topical agents, including multiple action agents, corticosteroids, and immunophilins, are used in stages and in combination. Surgery (ie, corneal transplantation) would be required for those developing severe keratoconus. LASIK surgery is not recommended in these patients. Modified from Sy and Bielory.[3]

dermatitis, rhinitis, sinusitis, and asthma. Avoidance of allergens is an important starting strategy, but for the ocular involvement, the mainstay of treatment includes topical medications. Oral medications are indicated in only very severe cases. Current topical medications for allergic conjunctivitis include lubricants, topical antihistamines, mast cell stabilizers, eosinophil deactivators, and anti-inflammatory agents such as steroidal and nonsteroidal anti-inflammatory drug drops. Topical corticosteroids are the cornerstone of treatment to control the acute phase of AKC.

The management of AKC is difficult, and patients cannot be cured. Allergic conjunctivitis, especially chronic forms, are associated with dry eye syndromes (dry eye syndromes are associated with hyperosmolarity, or a higher sodium content, in the tear film),[11–13] whereas seasonal allergic inflammation does not appear to be associated with permanent tear film instability.[14] Ophthalmic preservatives may aggravate ocular allergies, with the possibility of developing an allergic response,[15] and may cause cytotoxicity of the conjunctival epithelium.[16] Because antihistamines also demonstrate anticholinergic activity (especially older forms of antihistamines), these will actually worsen dry eye symptoms while improving the nasal symptoms of allergic rhinoconjunctivitis (Fig 2). It is crucial to control the facial eczema and lid margin inflammation.

Most ocular corticosteroids, including betamethasone, dexamethasone, fluorometholone, and hydrocortisone, have been used in the treatment of AKC but may increase intraocular pressure and increase the risk of cataracts and corneal infection through local immunosuppression. Long-term use of oral corticosteroids, such as prednisone, is more commonly associated with increased intraocular pressure and cataracts. They also may delay wound healing.[2,17] Notable in the present patient is a family history of glaucoma which may predispose this patient to developing increased intraocular pressure.

Loteprednol is the only topical steroid (it also is available as a gel) approved for allergic conjunctivitis that can be used by allergists and clinical immunologists. Other formulations of ophthalmic steroids have a greater penetration into the eye with increased potential for increasing intraocular pressure and with this patient's family history of glaucoma raises that concern.[8] The long-term use of topical corticosteroids (>10 days) should warrant a referral to the ophthalmologist (Table 3). Ointment or gel applied at night-time is an alternative when ophthalmic drops cannot be used.[2] Systemic cyclosporine use for AKC has been limited to small studies but appears to be effective as a steroid-sparing agent, with doses of 50 to 300 mg (up to 5 mg/kg) daily (in divided doses) given for several months.[18,19] Surgical treatment or tarsal conjunctival resection may be required for conjunctival papillary hyperplasia aggravating the corneal ulcers, whereas surgical curettage may be needed for corneal plaques. The administration of autologous fibronectin eye drops has been shown to ameliorate inflammation and resurface the corneal epithelium.[20] Amniotic membrane implantation has been used to re-epithelialize the corneal ulcers of chronic AKC.[21,22]

Allergen immunotherapy is beneficial in patients with AKC to decrease future allergic symptoms by increasing the threshold to the allergens associated with the ocular and nasal signs and symptoms. Immunomodulation for inflammation related to dry eye disease and AKC includes topical cyclosporine and potentially omalizumab and other immunophilins that have been used in treatment and selective glucocorticoid receptor antagonists and nanoparticles.[23]

LASIK surgery has been noted to lead to increased complications in patients with ocular allergies, particularly those with AKC.[24] However, some patients with AKC require corneal surgery for keratoconus, which, in the presence of AKC, is a high-risk procedure.

Conclusion

AKC in general refers to a chronic and aggressive form of allergic conjunctivitis with sight threatening fibrosis most often seen in adult patients with atopic dermatitis, asthma and allergic rhinitis. AKC commonly involves the eyelid, conjunctiva and cornea. Involvement is commonly bilateral although its severity may be disproportionately distributed to one side. Blepharitis and dry eye syndromes commonly complicate the inflammatory response of the ocular surface.

Learning Points

- Atopic keratoconjunctivitis is one of several forms of chronic inflammatory disease of the anterior surface of the eye and eyelid that is at the severe end of a spectrum of allergic conjunctival diseases.
- Atopic keratoconjunctivitis can involve the cornea and conjunctiva bilaterally and at times can lead to visual loss from corneal complications.
- Long-term involvement of the eyelids (blepharitis) is common and is an important component of the treatment intervention.
- Tear film abnormalities with hyperosmolarity are noted in chronic allergy, consistent with dry eye syndromes.
- Referral to an ophthalmologist should occur if a patient has used ocular corticosteroids for persistent ocular complaints, the consideration of strong topical or systemic corticosteroids, and the presence of ciliary flush.
- Current treatment options include a stepwise, multidisciplinary approach that involves medical interventions with topical and systemic immunomodulating agents and surgery (corneal transplantation) for keratoconus.

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